REMARKS

Summary of the Invention

The present invention features the discovery of the mammalian methionine synthase reductase gene. The methionine synthase reductase gene encodes a protein which catalyzes the reductive methylation of methionine synthase-cob(II)alamin to generate methionine synthase-cob(III)alamin-CH3, thereby maintaining methionine synthase in its reduced, activated state. Mutations in the methionine synthase reductase gene have been discovered to be associated with neural tube defects, cardiovascular disease, and cancer. The invention provides wild-type and mutant mammalian methionine synthase reductase nucleic acid molecules and their complements.

Summary of the Telephonic Interview

Applicants wish to thank the Examiner and the Examiner's supervisor for their helpful comments during the telephonic interview conducted on September 7, 2004. During the telephonic interview, Applicants discussed the 35 U.S.C. § 112 first and second paragraph rejections of claims 1-2, 4-5, 36-37, 41-43, 45-47, and 52-53, and claims 5, 41-43, 45-46, 52-55, respectively. A discussion of each of the interview topics is provided below.

Summary of the Office Action

Claims 1-5, 36-38, 41-43, 45-49, and 52-55 are pending. Claims 48 and 49 are withdrawn from consideration as being drawn to a non-elected invention. Claims 5, 41-43, 45-46, and 52-55 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness, while

claims 1-2, 4-5, 36-37, 41-43, 45-47, and 52-53 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. By this reply, Applicants cancel claims 1-5, 36-38, 41-43, 45-47, and 52-55, add new claims 56-70, and address each of the Examiner's rejections.

Support for the Amendment

Support for new claims 56-70 is found in prior claims 1-5, 36-38, 41-43, 45-47, and 52-55 and in the specification on, e.g., page 5, line 5, through page 6, line 11, page 7, lines 7-17, page 13, line 18, through page 14, line 16, page 16, lines 2-10, page 18, lines 9-17, and page 22, lines 14-18. No new matter is added by the amendment. Applicants provide the following table of correspondence to show the Examiner where support for each claim is derived.

Table of Correspondence

Claim	Support
56	Prior claims 1, 3, and 36-38; page 16, lines 2-10; and page 18, lines 9-17, of the specification
57	Prior claims 1, 3, and 36-38; page 5, lines 5-11, of the specification
58	Prior claims 1, 2, 3, and 36-38; page 5, lines 5-11, of the specification
59	Prior claims 1, 36, and 45; page 16, lines 2-10, of the specification
60	Prior claims 1, 36, 45, and 46; page 16, lines 2-10, of the specification
61	Prior claims 1, 36, and 47-49
62	Prior claims 36 and 54
63	Prior claims 3 and 36-38; page 7, lines 10-17; page 16, lines 2-10; and page 18, lines 9-17, of the specification
64	Prior claims 3 and 36-38; page 7, lines 10-17, of the specification
65	Page 6, lines 1-3, of the specification
66	Prior claims 47-49
67	Prior claims 36 and 54
68	Prior claims 41-43; page 5, lines 15-25; page 17, line 6, through page 18, line 1; page 18, lines 9-17; and page 22, lines 14-18, of the specification.
69	Prior claims 1, 36, and 47-49
70	Prior claims 36 and 54

Rejections under 35 U.S.C. § 112, second paragraph

Claims 5, 41-43, and 52-53, and 55

Claims 5, 41-43, 45-46, and 52-55 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failure to distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that claims 5, 41-43, and 52-53, and 55 "are indefinite in the recitation of 'complementary' and 'complement' because it is unclear which 'complements' are encompassed by the claims. Applicants have not define[d] the term 'complement', as is relates to size..." (Office Action, p. 2).

During the telephonic interview, the Examiner indicated that this rejection could be overcome by replacing the term "complementary" with "completely complementary" to clarify that the recited nucleic acid sequence was complementary over the entire sequence of SEQ ID NO: 1, 41, 43, 45, or 47. In response, Applicants have cancelled claims 5, 41-43, 52-53, and 55, and have provided new claims 68-70, which are directed to an antisense nucleic acid molecule in which the nucleic acid sequence is "completely complementary" across the indicated sequence of SEQ ID NOs: 1, 41, 43, 45, or 47. Based on the Examiner's remarks in the Office Action and during the telephonic interview of September 7, 2004, Applicants believe that new claims 68-70 do not lack clarity with respect to which "complements" are encompassed by the claims. Therefore, this rejection should be withdrawn and should not be applied to new claims 68-70.

Claims 45 and 46

Claims 45 and 46 are rejected for reciting the term "biological activity" without defining

that activity in the claims. In the Office Action, the Examiner suggests amending the claims to recite that the nucleic acid molecule encodes a "mammalian methionine synthase reductase polypeptide having at least [X]% of the methionine synthase reductase activity of the methionine synthase reductase polypeptide of SEQ ID NO: 2" (Office Action, p. 3; Emphasis added). During the telephonic interview, the Examiner confirmed that inclusion of this clear definition for the intended biological function would overcome this rejection. Therefore, new claims 59 and 60, which correspond to cancelled claims 45 and 46, respectively, have substituted the term "biological activity" with "at least 55%" and "at least 20%" "methionine synthase reductase activity," respectively. Accordingly, Applicants respectfully request that the rejection of claims 45 and 46 be withdrawn and should not be applied to new claims 59 and 60.

Claims 53 and 55

Claims 53 and 55 are rejected for indefiniteness for reciting a nucleic acid molecule having a polynucleotide sequence the complement of which comprises "a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism." The Examiner states that claims 53 and 55 do not require that the nucleic acid molecule is a mammalian methionine synthase reductase gene or that it has the function of a polypeptide encoded by such a gene. For this reason, the Examiner argues that it is unclear how the term further limits the claims. The Examiner notes that the rejection of claims 53 and 55 was not applied to claim 54.

Applicants have cancelled claims 53 and 55, and now provide new claim 70, which recites that the antisense nucleic acid molecule comprises a polynucleotide sequence the complete complement of which comprises a mutation or polymorphism present in a naturally-

occurring mammalian methionine synthase reductase gene. Accordingly, new claim 70 clarifies that the mutation or polymorphism is naturally-occurring and is found in a mammalian methionine synthase reductase gene. Thus, new claim 70 addresses both issues raised by the Examiner, and the rejection of claims 53 and 55 can be withdrawn and should not be applied to new claim 70.

Rejections under 35 U.S.C. § 112, first paragraph

Enablement

Claims 1-2, 4-5, 36-37, 41-43, 45-47, and 52-53 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. In the final Office Action dated May 19, 2004, the Examiner states that the specification is enabling for claims 3 and 38, which are directed to a nucleic acid molecule that has 100% and 95% sequence identity to SEQ ID NO: 1, 41, 43, 45, or 47, respectively, but that the specification is not enabling for a nucleic acid molecule that has 50%, 85%, or 90% sequence identity to SEQ ID NO: 1, 41, 43, 45, or 47, or to the complement thereof, as is recited in claims 1-2, 4-5, 36-37, 41-43, 45-47, and 52-53 (Office Action pp. 4 and 7). The Examiner reiterated this position during the telephonic interview of September 7, 2004.

Applicants respectfully disagree, but in an effort to expedite prosecution of the application, Applicants have cancelled claims 1-5, 36-38, 41-43, 45-47, and 52-53 and now provide new claims 56-58 and 63-65, which correspond to prior claims 3 and 38 deemed allowable by the Examiner in the final Office Action dated May 19, 2004 and during the telephonic interview of September 7, 2004. Because claims 56-58 and 63-65 are directed to subject matter that the Examiner has deemed allowable, Applicants respectfully request that the

rejection of claims 1-2, 4-5, 36-37, 41-43, 45-47, and 52-53 under 35 U.S.C. § 112, first paragraph, be withdrawn and that the rejection should not be applied to new claims 56-58 and 63-65.

Applicants also provide new claims 59-62, which depend from new claim 56, and new claims 66-67, which depend from new claim 63. New claims 59-62 and 66-67 correspond to prior claims 45-47 and 52. Claims 59 and 60 are directed to a nucleic acid molecule with at least 95% sequence to SEQ ID NO: 1 and encoding a mammalian methionine synthase reductase polypeptide that has at least 20% (claim 59) or 55% (claim 60) of the methionine synthase reductase activity of the methionine synthase reductase polypeptide of SEQ ID NO: 2. Claims 61 and 66 recite that the nucleic acid molecule of claim 56 and 63, respectively, further comprises a consensus binding site for one or more cofactors selected from the group consisting of FAD, FMN, and NADPH, in which the sequence of the binding site is selected from any one of SEQ ID NOs: 25 or 52-61. As discussed during the telephonic interview of September 7, 2004, Applicants have limited the sequences recited in claims 61 and 66 to those that correspond to cofactor binding sites that are naturally present in the methionine synthase reductase polypeptide encoded by SEQ ID NOs: 1, 41, 43, 45, and 47. Finally, claims 62 and 67 specify that the nucleic acid molecule of claim 56 and 63, respectively, comprises a mutation or polymorphism present in a naturally-occurring mammalian methionine synthase reductase gene.

Because claims 59-62 and 66-67 depend from, and further limit the subject matter of, independent claims 56 and 63, respectively, which the Examiner has deemed to be allowable, Applicants respectfully submit that dependent claims 59-62 and 66-67 are also in condition for allowance and respectfully request that the rejection of claims 45-47 and 52 be withdrawn and

that the rejection not be applied to new claims 59-62 and 66-67.

The Examiner also states that the specification is not enabling for a nucleic acid molecule that hybridizes under specific conditions to the polynucleotides of SEQ ID NO: 1, 41, 43, 45, or 47, or that corresponds to the complete complement of a polynucleotide sequence having at least 50%, 85%, or 95% sequence identity to SEQ ID NOs: 1, 41, 43, 45, or 47, where the nucleic acid molecule is capable of reducing the expression of methionine synthase reductase polypeptide, as is recited in claims 4, 5, 41-43, 52, and 53 (Office Action, p. 4). Applicants respectfully disagree, but have cancelled claims 4, 5, 41-43, 52, and 53 and now provide new claims 68-70, which are directed to an antisense nucleic acid molecule that has a polynucleotide sequence that is completely complementary to at least 18 contiguous nucleotides of a mammalian methionine synthase reductase gene having the polynucleotide sequence of SEQ ID NOs: 1, 41, 43, 45, or 47. Present claims 68-70 are enabled by the specification.

The specification discloses and enables antisense nucleic acid molecules that are completely complementary to at least 18 contiguous nucleotides of a mammalian methionine synthase reductase gene having the polynucleotide sequence of SEQ ID NO: 1, 41, 43, 45, or 47 (see, e.g., page 5, lines 15-25, page 10, lines 5-12, and page 22, lines 14-18, of the specification). Furthermore, as was discussed in the previous Reply to Office Action, filed on March 2, 2004, the specification provides considerable guidance for how to use an antisense molecule of claims 68-70. For example, at page 35, line 15, through page 36, line 20, the specification teaches the use of an enzyme-linked immunosorbant assay (ELISA) for determining whether a compound (e.g., an antisense nucleic acid molecule) is able to modulate the level of expression of a methionine synthase reductase polypeptide. Page 37, lines 1-18, of the specification describes

the use of a quantitative PCR assay for determining the ability of a compound to modulate the level of a methionine synthase reductase polypeptide (i.e., by detecting the amount of mRNA levels in a sample). Therefore, the specification provides the skilled artisan with sufficient guidance to make and use the invention recited in claims 68-70.

Furthermore, as is discussed above, the Examiner concedes that the specification is enabling for nucleic acid molecules having at least 95% sequence identity to the polynucleotide sequence of SEQ ID NOs: 1, 41, 43, 45, or 47. It is well within the purview of one skilled in the art to prepare antisense molecules that are complementary to such nucleic acid molecules as this technology was well known in the art prior to Applicants' priority date of January 16, 1998 and would require nothing more than routine experimentation (see, e.g., Moroni et al., J. Biol. Chem. 267:2714-2722, 1992; a copy of which is provided as Exhibit A). Therefore, because the specification enables any person skilled in the art to make "sense" strand nucleic acid molecules, the preparation of complementary "antisense" molecules recited in claims 68-70 must also be enabled by the specification. Accordingly, the rejection of claims 45-47, and 52 under 35 U.S.C. § 112, first paragraph, for lack of enablement should be withdrawn and should not be applied to new claims 68-70.

Written Description

In the Advisory Action, mailed on November 18, 2004, the Examiner states:

> Claims 65-68 and 73 [provided in the Reply to Final Office Action dated October 19, 2004] are directed to a genus of nucleic acids of <u>any</u> size which share <u>at best 18 contiguous nucleotides of polynucleotides which are between 2094-2097 nucleotides long</u> (SEQ ID NO: 1, 41, 43, 45, and 47), and decrease the expression of any methionine synthase reductase polypeptide. No information has been

> provided in regard to the structural elements required in the genus of antisense nucleic acids recited which would allow for the reduction of expression of any gene encoding a methionine synthase reductase. Advisory Action dated November 18, 2004; emphasis in original.

Applicants have modified prior claims 65-68 and 73 submitted in the Reply to Final Office Action dated October 19, 2004, which are now provided as new claims 68-70. New claims 68-70 are directed to an antisense nucleic acid molecule that has a polynucleotide sequence that is completely complementary to at least 18 contiguous nucleotides of a mammalian methionine synthase reductase gene having the polynucleotide sequence of SEQ ID NOs: 1, 41, 43, 45, or 47. Because the nucleic acid sequences of SEQ ID NOs: 1, 41, 43, 45, and 47 are provided by the instant specification, the genus of antisense nucleic acid molecules corresponding to the complete complement of SEQ ID NOs: 1, 41, 43, 45, and 47, and comprising at least 18 contiguous nucleotides, is described by the specification. Therefore, Applicants submit that claims 68-70 do not lack written description and a rejection under 35 U.S.C. § 112, first paragraph, for lack of written description, should not be applied to new claims 68-70.

For all of the reasons discussed above, the specification provides considerable written description and enabling guidance to the skilled artisan for practicing the full scope of new claims 56-70. Therefore, Applicants respectfully request that the rejection of claims 1-2, 4-5, 36-37, 41-43, 45-47, and 52-53 under 35 U.S.C. § 112, first paragraph, should be withdrawn and should not be applied to new claims 56-70.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a petition to extend the period for replying for two months, to and including February 22, 2005 since February 19, 2005 falls on a Saturday and February 21, 2005 falls on a Federal holiday.

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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